# REMARKS

Claims 33-51 are pending before entry of this amendment. In response to the office action mailed June 1, 2004, applicant amends the claims and provides arguments for patentability over the cited references. Amendments have not added new terms and no new matter has been added. The term "satellite myoblast cells" in claims 34 and 43 has been re-written as "satellite cell myoblasts" for the sake of greater clarity. The term "more than" added to claim 46, is supported, for example, by the term "more than" in claim 37 and page 12, lines 12-13 of the specification. The term "between" in claim 33 has been replaced by "close to" and is supported by grammatical context, as well as the specification, for example, on p. 13 lines 6-7. The term "patient's" has been replaced with "donor's" in claims 34 and 43 to clarify an otherwise logical inconsistency pointed out by the Examiner.

Reconsideration and allowance of the claims are courteously solicited.

Information Disclosure Statement

On page 2 of the office action, the Examiner has argued that only 6 references were noted in an IDS but that 12 documents were provided. Applicant thanks the Examiner for making this observation and is preparing another IDS.

Objection to claims 33-51

The Examiner has objected to the claims as reciting a non-elected invention. In response, applicant deletes the term "or that interferes with binding of substance P to its receptor" from claim 33 and from claim 42. Removal of this objection is solicited.

35 USC 112 second paragraph rejection of claims 33 and 42

From the bottom of page 2 through page 3, the Examiner argues that the term "allogeneic cells" is incompatible with the patient as the source of the cells. In response, applicant has deleted the phrase "from the patient" for clarification of claims 33 and 42. Reconsideration and removal of this rejection are solicited.

The Examiner argues on the top of page 3 that a patient's own cells are not allogenic. In response, the term "patient" has been replaced with "donor." Reconsideration and allowance are requested.

35 USC 103 rejection of claims 33-51

On pages 3 to 6 the Examiner has rejected the claims based on an obviousness argument "over Wu et al..... in view of Beutler.... and others.

The Examiner has admitted on page 4, lines 7-8 that "the art does not teach administration of myoblasts expressing a peptide that binds to opioid receptor to a muscle for treating pain."

On the other hand, the Examiner argues that "it was routine to use myoblasts for ex vivo gene therapy for treating diseases and providing recombinant therapeutic proteins in an animal." However, this was not routine. Even the cited papers evince this fact. The cited papers describe studies on mice (not human) myoblasts that were novel and pioneering enough to merit the status of publication as research papers to stimulate debate and discussion on how to address this difficult research issue. For example, the main reference of Wu emphases its value as providing "a useful model to study the biological properties of beta-endorphin and enkephalins," (last sentence, second to last paragraph).

Furthermore, no successful human work is cited. Applicant is unaware of any medically approved procedure anywhere in the world that even promised to offer ex vivo gene therapy this way. The claims recite human (patient) use, and not mouse use or other

animal use. Applicant's claims do not cover the research tools proposed by the cited research.

The cited references differ both in technique, materials and results. The claims recite the different materials of human allogenic muscle cells. These are not the same or similar to Deglon's differentiated myoblasts, and in fact, applicant has not attempted to cover Deglon's different material. Encapsulation techniques and intrathecal administration are not relevant. Law, 1996 teaches the now well known fact that myoblasts may be added to an animal's muscle. However, the claimed invention is not directed to myoblast therapy per se and the claims recite a novel and unobvious combination that produces unexpected results.

**The Claimed Combination Proves Desirable, Unexpected Advantage**

The claims recite methods for obtaining allogenic cells, manipulating those cells to incorporate a specific kind of expressed transgene, and then implanting those altered cells into a very special type of organ located at a very special type of location to take advantage of a very special type of delivery.

The closest cited art of Wu teaches the research and study value of inserting "clonal cell line" (first page, right middle column) that secrete opioids "for the study of tolerance." The claimed invention does not use clonal cell lines, which behave fundamentally differently, and are dangerous to implant into patients. The claimed invention is not a research tool, and in fact solves a problem (formation of tolerance due to continuous release of opioid) that was addressed by the research paper. The research paper did not suggest or discover the solution as now claimed by applicant.

The Wu reference admits a fundamental problem in this area, which the Examiner has not discussed, which is that "the development of tolerance reduces the effectiveness of drug therapies and requires escalated doses that can contribute to opioid side effects" (sentence bridging pages 1 and 2). Furthermore, this reference teaches that

"Mice receiving cell implants developed tolerance to opiods." Thus, cells that make opioids and delivered to body spaces are undesirable, giving bad results.

In contrast, the claimed invention and the embodiments taught, rely on three explicit and inherent properties of the novel claimed method. One, (as claimed) the method integrates opioid producing cells into existing muscle mass. In fact, the cells fuse and become one with such mass. These cells behave very differently than the cells transplanted by Wu and others into body spaces. Two, (as claimed) the method uses muscles near the CNS (not spaces near the CNS). Three, (inherent feature as claimed) the method relies on muscle contraction to deliver opioid to the CNS when neck muscles are under stress. That is, when stressed, the treated muscles deliver more opioid, compared to the relaxed condition. The cited reference(s) rely on adding the opioid producing cells to a body mass in a manner that does not provide such inherent modulation of delivery. Although the claimed method provides fairly continuous synthesis of opioid, as described in the specification, the actual delivery of opioid outside of the muscle to receptors is modulated by the combination of a. fused myogenic cell delivery system; b. targeting of neck muscles; and c. alterations in opioid efflux with increased efflux during times of extreme muscle stress. During extensive work on muscle repair, applicant has learned that efflux of muscle cell contents is increased during stress. Without wishing to be bound by any one theory of this embodiment of the invention, it is believed that this principle is responsible for the greatly attenuated developed tolerance with the claimed procedure expected over that cited in the references.

Applicant points out that merely administering opioid per se to a patient is well known but has a fundamental problem of opioid tolerance. Until now, there has been no method for allowing in vivo transgenic administration of opioid in a manner wherein opioid is delivered in higher amounts during periods of stress compared to a regular

baseline. This inherent feature is not anticipated by an reference and has not been predicted or described.

Reconsideration and allowance of the amended claims is solicited.

**Other differences from the cited art**

The claimed invention differs several ways from the cited art. Wu's "implantation" of mouse cell lines that are expressed in mouse spinal cord (page 4 top, office action) is not analogous to the claimed invention. As explained in the specification (p. 4 lines 2-5 for example) implantation into spinal cord is extremely dangerous, undesirable, and leads to very different results. Wu had no integration into muscle tissue. The secretion routes of opioid are very different. Beutler's fibroblasts are not comparable. In fact, applicant has found that transplantation of fibroblasts is to be avoided in his system. Intrathecal grafting of beta endorphin secreting fibroblasts is not the same as the claimed invention. The intrathecal administration of cells in a capsule is totally different as well, and lacks the inherent advantages of the invention as claimed. The factors cited by the Examiner on page 4 (bottom) including use of non-human cells, encapsulation and subsequent survival for over three months do not relate to the claimed system wherein introduced cells fuse with existing tissue and become permanent.

The use of chosen muscles from the neck is not obvious, except from a hindsight analysis. Applicant is unaware of any prior art that would provide motivation for this, particularly with the combination claimed. Applicant notes in this regard the lack of any description of neck muscle contents being available more readily to non-muscle tissues during times of stress.

Reconsideration and allowance are requested.

**Other claim**

Applicant points out that the conversion of transgenic cells into fat cells in vivo is safer and has value, for example, as described on page 7 lines 7-10. Claim 42 recites this embodiment. Consideration and allowance of this claim specifically is requested.

Respectfully submitted,

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Marvin A. Motsenbocker
Attorney for Applicant
Reg. No.: 36,614

Heller Ehrman White & McAuliffe LLP
1666 K Street, N.W., Suite 300
Washington, D.C. 20006-4004
Telephone: (202) 912-2000
Facsimile: (202) 912-2020

Customer No. 26633